SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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VERSION 2.0 (DECEMBER 2014)

Item #	Section/Subsection/Item	Description	Check for approval
	A. General		
1.	Title of the review	Neurotransmitters and metabolites in brain microdialysates under sleep, circadian rhythms and sleep deprivation conditions – A systematic review	
2.	Authors (names, affiliations, contributions)	Julia Menon Rob B.M. de Vries W.H. (Pim) Drinkenburg Cathalijn Leenaars	
3.	Other contributors (names, affiliations, contributions)	-	
4.	Contact person + e-mail address	Cathalijn.Leenaars@radboudumc.nl	
5.	Funding sources/sponsors	None	
6.	Conflicts of interest	None	
7.	Date and location of protocol registration	20-10-2017, SYRCLE website	
8.	Registration number (if applicable)		
9.	Stage of review at time of registration	Title-abstract screening in progress	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Sleep is a natural phenomenon that takes up about one third of our daily time. In humans, it is divided in 5 stages (sleep stage 1-4 and Rapid Eye Movement (REM) sleep), while in *e.g.* rats usually 2 stages are identified (Slow Wave Sleep (SWS) and REM-sleep). It enables essential biological processes such as restoration, memory processing and synaptic plasticity/homeostasis. Surveys show that the number of people being sleep deprived has risen over the last decades, and is now affecting 20% of the population[1]. This public health issue affects cognition (*e.g.* problems with memory, attention, planning, and coordination tasks) and is related to conditions such as diabetes, cardiovascular disease, depression, and obesity[1]. Causes for sleep deprivation (SD) are multifactorial, ranging from sleep apnoea, to acute anxiety and mental illnesses. Although the behavioural effects of SD are well known, sleep regulation and its molecular mechanism - notably during SD - remain largely obscure due to their complexity. The sleep-wake states are orchestrated by a complicated network of interconnected brain structures and their neurochemistry, influenced by external cues around the clock and responding to endogenous sleep inducing factors. The drivers of these mechanisms are on one side homeostatic processes and on the other circadian rhythms that together manage the intensity and the timing of sleep[2]. Homeostatic processes can intervene after a prolonged time awake due to hypogenic substances (*e.g.* accumulation of adenosine), which drives the organism to sleep and compensates for any sleep loss[3]. The circadian rhythm is represented in an internal clock that ensures physiological and behavioural actions to occur at the most appropriate time, for instance producing corticosterone and other hormones, sleeping, or waking up. The centre of the biological clock , the suprachiasmatic nucleus (SCN), is influenced by light, which affects melatonin level	

		(a sleep inducing hormone in diurnal animals)[2]. The SCN interconnects with the sleep-state generator: the ventrolateral preoptic area (VLPO). The latter possesses GABAergic neurons that inhibit wake-promoting regions, and thus induce sleep[4]. In addition to the VLPO, the reticular activating system (RAS) promotes wakefulness by activating cortical regions and inhibiting the VLPO during the active phase[2, 4, 5]. Two branches compose the RAS, one with cholinergic neurons and the second with monoaminergic (i.e. noradrenergic, serotonergic, dopaminergic, ...) neurons [2, 4, 5]. Earlier models of brain circuitry controlling wake–sleep focused primarily on monoaminergic and cholinergic arousal systems. More recently it has been suggested that these play a crucial modulatory role, whereas the backbone of the wake–sleep regulatory system would depend upon fast neurotransmitters, such as glutamate and GABA[6] Thus, low levels of RAS' neurotransmitters are expected during sleep, and higher levels during wake. However, some of the wake-promoting neurotransmitters, like dopamine, are required in sleep[7]. Neurotransmitters, their fluctuations, and their complex modulatory interdependencies are the key effectors in regular sleep, which makes them of high interest to study during sleep and SD. Microdialysis is one of the most versatile techniques to quantify multiple neurotransmitters and metabolites simultaneously, *in vivo,* in the interstitial fluid within a defined area (*e.g.* in the dorsal striatum, prefrontal cortex)[8]. With this review, we aim to increase our understanding of the intricate neurochemical mechanisms and interactions involved in sleep, circadian rhythms, and SD, focussing on the monoaminergic neurotransmitters, by collecting all available data from microdialysis studies on these monoaminergic neurotransmitters and their metabolites: adrenaline, noradrenaline, dopamine, serotonin, DOPAC, 5-HIAA, and 5-HPT. This review should enable us to correlate neural pathways to sleep-wake behaviour and assess their relevance.	
	Research question		
11.	Specify the *conditions of interest*	Sleep disturbances	
12.	Specify the population/species studied	All animals including humans	
13.	Specify the intervention/exposure	Regular Sleep, circadian rhythms at baseline, sleep disorders and sleep deprivation	
14.	Specify the control population	Any or none (for baseline measurements of sleep and circadian rhythms)	
15.	Specify the outcome measures	Concentration of dopamine, noradrenaline, adrenaline, serotonin and certain of their metabolites 5-HIAA, 5-HTP, and DOPAC in brain dialysates	
16.	State your research question (based on items 11-15)	What is the effect of sleep, circadian rhythms, sleep disorders and sleep deprivation on the levels of dopamine, noradrenaline, adrenaline, serotonin and their metabolites 5-HIAA, 5-HTP, and DOPAC as measured by brain microdialsysis in humans and other animals?	
	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	X MEDLINE via PubMed ☐Web of Science ☐SCOPUS X EMBASE ☐Other, namely:	

		☐Specific journal(s), namely:	
18.	Define electronic search strategies (*e.g.* use the step by step search guide[15] and animal search filters[20, 21])	The search strategy is available below the protocol's table	
19.	Identify other sources for study identification	☐Reference lists of included studies ☐Books ☐Reference lists of relevant reviews ☐Conference proceedings, namely: ☐Contacting authors/ organisations, namely: XNone	
20.	Define search strategy for these other sources	-	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	1. title/abstract screening 2. full text screening	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	a) Two independent reviewers per screening phase b) Discussion until consensus is reached, decision by a 3rd person if no consensus is reached	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: Primary study measuring the neurotransmitters or metabolites of interest a. During sleep deprivation, or b. During various sleep stages, or c. In models of sleep disturbances, or d. During prolonged baseline for circadian rhythms; defined as more than 6 hours and including at least one transfer between light and dark phase. Exclusion criteria: Other types of study, review not including new data	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: any animal, including humans Exclusion criteria: *In vitro* studies	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Any or none	
26.	Outcome measures	Inclusion criteria: dopamine AND/OR adrenaline AND/OR noradrenaline AND/OR serotonin AND/OR 5-HIAA AND/OR 5-HTP AND/OR DOPAC concentration in brain dialysates Exclusion criteria: none of these compounds measured, or measured with different method.	
27.	Language restrictions	Inclusion criteria: Any Exclusion criteria: -	
28.	Publication date restrictions	Inclusion criteria: Any Exclusion criteria:	
29.	Other	Inclusion criteria: -	

		Exclusion criteria:	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase: Screening titles/abstract 1. No microdialysis and/or microdialysis of other compounds than dopamine, noradrenaline, adrenaline, serotonin, 5-HIAA, 5-HTP and DOPAC 2. Extracerebral dialysis 3. *In vitro* studies Selection phase: full text 1. No microdialysis 2. No measure of the following neurotransmitters or metabolites: dopamine AND/OR adrenaline AND/OR noradrenaline AND/OR serotonin AND/OR 5-HIAA AND/OR 5-HTP AND/OR DOPAC in dialysates 3. Extracerebral dialysis 4. *in vitro* studies 5. no measurements during sleep deprivation, during various sleep stages, in models for sleep disorders, and/ or during prolonged baseline for circadian rhythms	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	- Authors - Year - Title - Journal - Language - Research department - Laboratory location (country + city)	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	- Experimental groups (dependent or independent) - Number of animals per group	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	- Animal species/strains - Age/weight - Sex - Dark-light regime	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	- Sleep deprivation timing - Baseline measurements time - Type of sleep stage determination - Type of sleep disturbance model	
35a.	*Measurement characteristics*	- Flow rate - Probe length - Probe / membrane type - Probe location (brain area) - Re-use of probe and/or animal - Washout time - Type of anaesthesia/freely behaving - Dialysate matrix (e.g. aCSF vs ringer) - Type of sample analysis used (HPLC, etc.) - Histological verification	
35b.	Outcome measures	Measured neurotransmitter in brain dialysates (converted to nmol/ml or % of baseline) during: - Baseline (circadian or model)	

		- specific sleep stages - sleep deprivation	
36.	Other (*e.g.* drop-outs)	Number of drop outs and reason, number of missing samples and reason (e.g. blocked flow).	
	Assessment risk of bias (internal validity) or study quality		
37.	Specify (a) the number of reviewers assessing the risk of bias/study quality in each study and (b) how discrepancies will be resolved	(a) 1 reviewer; a random sample of 5% of the included studies will be checked by a second reviewer. (b) Discussion between reviewers	
38.	Define criteria to assess (a) the internal validity of included studies (*e.g.* selection, performance, detection and attrition bias) and/or (b) other study quality measures (*e.g.* reporting quality, power)	☐By use of SYRCLE's Risk of Bias tool[4] ☐By use of SYRCLE's Risk of Bias tool, adapted as follows: ☐By use of CAMARADES' study quality checklist, e.g [22] ☐By use of CAMARADES' study quality checklist, adapted as follows: X Other criteria, namely: Extracted study characteristics (31-35) will be tabulated. This information (or lack of it) provides an indication of study quality, internal validity and risk of bias. The available risk of bias tools are not suitable to baseline measurements and within-subject comparisons.	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	Dialysate concentrations of dopamine, adrenaline, noradrenaline, serotonin, 5-HIAA, 5-HTP, and DOPAC in nM. Concentration units will be converted if needed in nM. If only % of baseline data are available then they will be extracted as such. When reported concentrations have been corrected for recovery, the actual concentrations in dialysates will be calculated.	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	- Data extraction from tables and text - If no numerical data are available in tables and/or text we will contact the authors - If no answers are received, digital image software or graphic rulers will be used to obtain data if they are available graphically.	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	a) 1 reviewer; a random sample of 5% of the included studies will be checked by a second reviewer. b) Discussion between reviewers	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	Results will be tabulated, grouped by neurotransmitters and metabolites, and by brain region of interest. They will be described qualitatively. Meta-analyses might be performed (refer to 43)	
43.	Specify (per outcome measure) how it	If at least 2 articles	

	will be decided whether a meta-analysis will be performed	-Have measures of the same neurotransmitter or metabolite in the same condition (i.e. sleep deprivation; sleep stage; sleep disturbance model and/ or circadian baseline) then a meta-analysis will be designed and performed.	
	If a meta-analysis seems feasible/sensible, specify (for each outcome measure):		
44.	The effect measure to be used (*e.g.* mean difference, standardized mean difference, risk ratio, odds ratio)	a. Sleep deprivation: Mean difference of % change from baseline within subjects b. Sleep-wake stages comparison or circadian baseline: standardized mean difference of the concentration in nM between conditions	
45.	The statistical model of analysis (*e.g.* random or fixed effects model)	The random effects model will probably be used as the microdialysis methods used in the different studies are expected to vary	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	I^2	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	Considered: Lab (microdialysis method is usually consistent within laboratories), species, sex, and experimental study design.	
48.	Any sensitivity analyses you propose to perform	-	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	For papers describing separate experimental groups, groups will be treated as independent experiments. If multiple baseline values are provided, the last one will be included in the analyses. If multiple measurements were made per animal, we conservatively assume a correlation of 1 between them, and calculate the mathematical average (Borenstein, Hedges *et al*)[9].	
50.	The method for assessment of publication bias	Considered: visual inspection of funnel plot.	
Final approval by (names, affiliations): Julia Menon, Cathalijn H.C Leenaars		Date: 20-10-17	

References:

1. Abrams, R.M., *Sleep Deprivation.* Obstet Gynecol Clin North Am, 2015. **42**(3): p. 493-506.
2. Foster, R.G. and L. Kreitzman, *Rhythm of life: The Biological Clocks that Control the Dayly Lives of Every Living Thing.* Yale University Press, New Haven and London, 2005.
3. Arias-Carrion, O., et al., *Biochemical modulation of the sleep-wake cycle: endogenous sleep-inducing factors.* J Neurosci Res, 2011. **89**(8): p. 1143-9.
4. FORT, P.-H.L.A.P., *Neurochemistry of sleep: an overview of animal experimental work.* Handbook of Clinical Neurology, Sleep Disorders, Part 1, 2011. **Vol. 98 (3rd series)**(chap 11): p. 173-190.
5. Murillo-Rodríguez, E., et al., *Basic Sleep Mechanisms An Integrative Review.* Central Nervous System Agents in Medicinal Chemistry, 2012. **12**: p. 38-54
6. Fuller, C.B.S.a.P.M., *Wake–sleep circuitry: an overview.* Current Opinion in Neurobiology, 2017. **44**: p. 186-192.
7. Dzirasa, K., et al., *Dopaminergic control of sleep-wake states.* J Neurosci, 2006. **26**(41): p. 10577-89.

8. Chefer, V.I., et al., *Overview of brain microdialysis.* Curr Protoc Neurosci, 2009. **Chapter 7**: p. Unit7 1.

9. Borenstein, M., et al. "Rothstein., HR, 2009. Introduction to Meta-Analysis." Chichester, UK, John Wiley & Sons, Ltd.

Search Strategy: PubMed

Sleep, Sleep deprivation and Circadian Rhythm:

Sleep and Sleep deprivation

sleep[MeSH] OR sleep*[tiab] OR sleep deprivation[MeSH] OR sleep stages[MeSH] OR (Rapid[tiab] AND eye[tiab] AND movement*[tiab]) OR parasleep[tiab] OR REM phase[tiab] OR non-REM[tiab] OR NREM[tiab] OR SWS[tiab] OR (light[tiab] AND dark[tiab]) OR sleep wake disorders[MeSH] OR dyssomnia*[tiab] OR jet lag*[tiab] OR time zone change*[tiab]

Circadian Rhythm:

periodicity[MeSH] OR circadian rhythm[MeSH] OR periodicit*[tiab] OR bioperiodicit*[tiab] OR rhythm[tiab] OR rhythmicit*[tiab] OR cyclicit*[tiab] OR biorhythm*[tiab] OR clock[tiab] OR clocks[tiab] OR oscillator[tiab] OR oscillators[tiab] OR biological pacemaker*[tiab] OR circadian[tiab] OR ultradian[tiab] OR diurnal[tiab] OR suprachiasmatic nucleus[MeSH] OR suprachiasmatic*[tiab] OR melatonin[tiab] OR baselin*[tiab]

Neurotransmitters and metabolites:

Dopamine and DOPAC:

Dopamine: catecholamines[MeSH] OR catecholamine*[tiab] OR catechol amine*[tiab] OR dopamine[MeSH] OR dopamin[tiab] OR dopamine[tiab] OR hydroxytyramin*[tiab] OR dihydroxyphenethylamin*[tiab] OR dihydroxyphenylethylamin*[tiab] OR dopaminerg*[tiab]
DOPAC: 3,4-dihydroxyphenylacetic acid[MeSH] OR dihydroxyphenylacetic acid[tiab] OR dihydroxyphenylacetate[tiab] OR dihydroxyphenethylamine[tiab] OR DOPAC[tiab]

Adrenaline:

epinephrine[MeSH] OR epinephrin*[tiab] OR adrenaline[tiab] OR adrenalin[tiab] OR adrenerg*[tiab]

Noradrenaline:

norepinephrine[MeSH] OR norepinephrin*[tiab]OR noradrenaline[tiab] OR noradrenalin[tiab] OR nor-adrenalin*[tiab] OR noradrenerg*[tiab]

Serotonin, 5-HPT and 5-HIAA:

serotonin: tryptamines[MeSH] OR tryptamine*[tiab] OR serotonin[MeSH] OR serotonin[tiab] OR serotonine[tiab] OR 5-HT[tiab] OR hydroxytryptamin*[tiab] OR hydroxy-tryptamin*[tiab] OR serotonerg*[tiab]
5-HTP: 5-Hydroxytryptophan[MeSH] OR hydroxytryptophan*[tiab] OR hydroxy l tryptophan*[tiab] OR hydroxy tryptophan*[tiab] OR 5-HTP [tiab]
5-HIAA: hydroxyindoleacetic acid[MeSH] OR 5HIAA[tiab] OR HIAA[tiab]OR hydroxyindoleacetic acid[tiab] OR 5-hydroxy-3-indoleacetic acid[tiab]OR hydroxy indoleacetic acid[tiab] OR hydroxyindole acetic acid[tiab] OR hydroxy indole acetic acid[tiab] OR 5-hydroxyindole-3-acetic acid[tiab] OR hydroxyindolacetic acid[tiab] OR hydroxy indolacetic acid [tiab] OR hydroxyindol acetic acid[tiab] OR hydroxy indol acetic acid [tiab] OR 5-hydroxyindol-3-acetic acid[tiab] OR hydroxyindolylacetic acid[tiab]

Microdialysis:

microdialysis[MeSH] OR micro dial*[tiab] OR microdial*[tiab] OR microD[tiab] OR

chemitrode[tiab] OR dialytrode[tiab] OR brain dialys*[tiab] OR intracerebral dialys*[tiab] OR cerebral dialys*[tiab] OR intracranial dialys*[tiab] OR transcranialdialys* [tiab]

Search Strategy: Embase

Sleep, Sleep deprivation and Circadian Rhythm:

Sleep and Sleep deprivation

exp sleep/ OR sleep*.ti,ab,kw. OR sleep disorder/ OR sleep stage/ OR (Rapid AND eye AND movement*).ti,ab,kw. OR parasleep.ti,ab,kw. OR REM phase.ti,ab,kw. OR (non-REM OR NREM).ti,ab,kw. OR SWS.ti,ab,kw. OR (light AND dark).ti,ab,kw. OR baselin*.ti,ab,kw. OR sleep disorder/ OR dyssomnia*.ti,ab,kw. OR jet lag syndrome*.ti,ab,kw. OR (time zone change syndrome* OR time zone syndrome*).ti,ab,kw.

Circadian Rhythm:

periodicity/ OR biological rhythm/ OR circadian rhythm/ OR (periodicit* OR bioperiodicit*).ti,ab,kw. OR (rhythm OR rhythmicit* OR biorhythm*).ti,ab,kw OR cyclicit*.ti,ab,kw. OR (clock OR clocks).ti,ab,kw. OR (oscillator OR oscillators).ti,ab,kw. OR biological pacemaker*.ti,ab,kw. OR circadian.ti,ab,kw. OR ultradian.ti,ab,kw. OR diurnal.ti,ab,kw. OR suprachiasmatic nucleus/ OR suprachiasmatic*.ti,ab,kw. OR melatonin.ti,ab,kw. OR baselin*.ti,ab,kw.

Neurotransmitters and metabolites:

Dopamine and DOPAC:

Dopamine: catecholamine/ OR (catecholamine* OR catechol amine*).ti,ab,kw. OR dopamine/ OR (dopamin OR dopamine OR hydroxytyramin* OR dihydroxyphenethylamin* OR dihydroxyphenylethylamin*).ti,ab,kw. OR dopaminerg*.ti,ab,kw.
DOPAC: 3,4-dihydroxyphenylacetic acid/ OR (dihydroxyphenylacetic acid OR dihydroxyphenylacetate OR dihydroxyphenethylamine OR DOPAC).ti,ab,kw.

Adrenaline:

epinephrine/ OR (epinephrin* OR adrenaline OR adrenalin OR adrenerg*).ti,ab,kw.

Noradrenaline:

noradrenalin/ OR (norepinephrin* OR noradrenaline OR noradrenalin OR nor-adrenalin* OR noradrenerg*).ti,ab,kw.

Serotonin, 5-HPT and 5-HIAA:

serotonin: tryptamine derivative/or tryptamine*.ti,ab,kw. OR serotonin/ OR (serotonin OR serotonine OR serotonin* OR 5-HT OR hydroxytryptamin* OR hydroxy-tryptamin*).ti,ab,kw. OR serotonerg*.ti,ab,kw.
5-HTP: 5 hydroxytryptophan/ OR (hydroxytryptophan* OR hydroxy l tryptophan* OR hydroxy tryptophan* OR 5-HTP).ti,ab,kw.
5-HIAA: 5 hydroxyindoleacetic acid/ OR (5HIAA OR HIAA OR hydroxyindoleacetic acid OR 5-hydroxy-3-indoleacetic acid OR hydroxy indoleacetic acid OR hydroxy indoleacetic acid OR hydroxyindolacetic acid OR hydroxyindole acetic acid OR hydroxy indole acetic acid OR OR 5-hydroxyindole-3-acetic acid OR hydroxyindolacetic acid OR hydroxy indolacetic acid OR hydroxyindol acetic acid OR hydroxy indol acetic acid OR 5-hydroxyindol-3-acetic acid OR hydroxyindolylacetic acid).ti,ab,kw.

Microdialysis:

microdialysis/ OR (micro dial* OR microdial* OR microD OR chemitrode OR dialytrode OR brain dialys* OR intracerebral dialys* OR cerebral dialys* OR intracranial dialys* OR transcranial dialys*).ti,ab,kw.